IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No. 10/720,831	Customer No. 23379
Applicant: Richard A. Berg	Confirmation No. 2955
Filed: Nov 24, 2003	Group Art Unit: 1652
Docket No. C94-018-D2	Examiner: Patterson, Charles L. Jr.

Title: *Mutated Recombinant Collagens*

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

We appeal from the Final Action dated Dec 18, 2006.

REAL PARTY IN INTEREST

The real party in interest is Angiotech Pharmaceuticals, Inc., the assignee of this patent application.

RELATED APPEALS AND INTERFERENCES

Appeals were filed in parent application Ser Nos. 08/278,774 (now, US Pat No 6,653,450), and 08/630,654 (abandoned) – the corresponding decisions are appended hereto. Appellants are unaware of other related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-5, 7-9, 14-16 and 18-20 are pending. Claims 18-20 are withdrawn. Claims 6, 10-13 and 17 are canceled. Claim 6 is shown pending and rejected in the subject Action; however, this claim was canceled by Appellant's Response dated Oct 23, 2006. We recognize that the dependency of claim 7 requires formal revision, an issue not on appeal, and that will be corrected on remand. Claims 4-5 stand rejected on the ground of nonstatutory obviousness-type double patenting, from which we are not appealing. Claims 1-3, 7-9 and 14-16 stand rejected

under 35USC112, first paragraph (enablement), which is the only pending rejection subject to this appeal.

STATUS OF AMENDMENTS

All Amendments are believed to be properly before the Board.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter is a recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first propeptide, and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide, and further comprising a second propeptide and a second non-natural site-specific proteolytic agent recognition site, wherein said second non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said second propeptide. Specification, p. 2, lines 29-35; Claim 1.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

I. WHETHER THE EXAMINER HAS PROPERLY REJECTED CLAIMS 1-3, 7-9 AND 14-16 UNDER 35USC112, FIRST PARAGRAPH (ENABLEMENT).

ARGUMENT

I. THE EXAMINER HAS NOT PROPERLY REJECTED CLAIMS 1-3, 7-9 AND14-16 UNDER 35USC112, FIRST PARAGRAPH (ENABLEMENT).

The appeal-from rejection consists of 3 sentences:

1. The instant specification teaches a recombinant procollagen chain that comprises a first natural C-terminal propeptide, not one comprising a first propeptide.

2. Many other propeptides fall within the metes and bound of "a first propeptide" besides "a natural C-terminal propeptide".

3. It is maintained that undue experimentation would be required to practice the instant invention within the limits of the instant claims.

First, these three sentences do not constitute a prima facie, reasoned case of non-enablement, and on that basis alone, the rejection should be reversed.

Second, even if a prima facie case is inferred, it does not withstand scrutiny – the first sentence is false on the record, making the third statement entirely unsupported.

The test for enablement is whether the specification enables one skilled in the art to practice the invention as claimed without undue experimentation. Here the Specification amply teaches and exemplifies a diverse variety of suitable propeptides in addition to the natural propeptide (e.g. Specification, p.5, lines 15-21; Example 2F at p.13, line 36 – p.14, line 21; Example 2G at p.14, lines 23-35). Following the guidance and exemplification of this disclosure one of ordinary skill in the art would have no difficulty practicing the claimed invention without undue experimentation, and there is no evidence or reason of record to the contrary.

Finally, it appears that the Examiner is in fact rejecting these claims for non-statutory reasons: "The parent application, 08/278,774, was allowed because the Board said that it was allowable. The examiner does not intend to allow broader claims than the Board ruled on."

Appellants respectfully request reversal of the Examiner's Final Action.

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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CLAIMS APPENDIX

1. A recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first propeptide, and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide, and further comprising a second propeptide and a second non-natural site-specific proteolytic agent recognition site, wherein said second non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said second propeptide.

2. A recombinant procollagen chain according to claim 1, wherein said first non-natural site-specific proteolytic agent recognition site is a site-specific protease recognition site.

3. A recombinant procollagen chain according to claim 1, wherein said first non-natural site-specific proteolytic agent recognition site comprises a peptide bond labile to chemical hydrolysis.

4. A recombinant procollagen chain according to claim 1, wherein said first propeptide is a C-terminal propeptide.

5. A recombinant procollagen chain according to claim 1, wherein said first propeptide is a natural procollagen C-terminal propeptide.

6. (canceled)

7. A recombinant procollagen chain according to claim 6, wherein said first and said second non-natural site-specific proteolytic agent recognition sites are different.

8. A recombinant procollagen chain according to claim 1, further comprising a non-natural amino acid sequence between said first site-specific proteolytic agent recognition site and said collagen chain.

9. A recombinant procollagen chain according to claim 1, further comprising a non-natural amino acid sequence between said first site-specific proteolytic agent recognition site and said first propeptide.

10-13. (canceled)

14. A recombinant collagen polypeptide chain produced by contacting a recombinant procollagen chain according to claim 1 with a first site-specific proteolytic agent capable of selectively cleaving said procollagen chain at said first site-specific proteolytic agent recognition site.

15. A collagen composition comprising a plurality of recombinant collagen chains according to claim 14, wherein said chains are polymerized.

16. A sterile, nontoxic, biocompatible collagen composition comprising a recombinant collagen chain according to claim 14.

17. (canceled)

18. A process for the production of a recombinant collagen polypeptide chain, said process comprising the steps of:

contacting a recombinant procollagen chain according to claim 1 with a site-specific proteolytic agent capable of selectively cleaving said recombinant procollagen chain at said first site-specific proteolytic agent recognition site under conditions wherein said first site-specific proteolytic agent selectively cleaves said procollagen chain at said first site-specific proteolytic agent recognition site, whereby a collagen chain is produced; and recovering said collagen chain.

19. (withdrawn) A method of promoting the growth of cultured cells on a solid substrate or the adherence of cultured cells to a solid substrate, said method comprising contacting said solid substrate with a composition according to claim 16.

20. (withdrawn) A method of augmenting localized tissue in a host, said method comprising the step of subcutaneously administering to a host a collagen composition according to claim 16.

RELATED PROCEEDINGS APPENDIX

The following three decisions in related proceeding are appended; no other decisions in any related proceedings are known to exist:

1. Decision on Appeal in 08/278,774;
2. Decision on Appeal in 08/630,654;
3. Decision by the US Court of Appeal for the Federal Circuit in 08/278,774 and 08/630,654.

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 33

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RICHARD A. BERG,
PAUL D. TOMAN and DONALD G. WALLACE

MAILED

APR 30 2001

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 1999-2231
Application No. 08/278,774

ON BRIEF

Before ADAMS, MILLS and GRIMES, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-3, 6-9, 14-16 and 18, which are all the claims pending in the application.

Claims 1 and 6 are illustrative of the subject matter on appeal and is reproduced below:

1. A recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide.

6. A recombinant procollagen chain according to claim 1, further comprising a second propeptide and a second non-natural site-specific proteolytic agent recognition site, wherein said second non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said second propeptide.

The references relied upon by the examiner are:

Olsen et al. (Olsen), "Purification and Characterization of a Peptide from the Carboxy-Terminal Region of Chick Tendon Procollagen Type I," Biochemistry, Vol. 16, No. 13, pp. 3030-3036 (1977)

Prockop et al. (Prockop), "The Biosynthesis of Collagen and its Disorders," New England Journal of Medicine, Vol. 301, No. 1, pp. 13-23 (1979)

Chu et al. (Chu), "Human proα1(I) collagen gene structure reveals evolutionary conservation of a pattern of introns and exons," Nature, Vol. 310, pp. 337-340 (1984)

Carter, "Site-Specific Proteolysis of Fusion Proteins," Protein Purification: From Molecular Mechanisms to Large-Scale Processes, Vol. 47, Chp. 13, pp. 181-193 (American Chemical Society 1990)

GROUND OF REJECTION[1]

Claims 1-3, 6-9, 14-16 and 18 stand rejected under 35 U.S.C. § 103 as being unpatentable over Chu, Prockop and Olsen in view of Carter.

We affirm the rejection of claims 1-3, 8, 9, 14-16 and 18. We reverse the rejection of claims 6 and 7.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the

[1] We note the examiner withdrew the Final rejection of claim 14 under 35 U.S.C. § 112, first and second paragraph. Answer, page 3.

appellants and the examiner. We make reference to the examiner's Answer[2], the examiner's reasoning in support of the rejections. We further reference appellants' Brief[3], and appellants' Reply Brief[4] for the appellants' arguments in favor of patentability. We note the examiner considered the Reply Brief, and entered it into the record.[5]

THE REJECTION UNDER 35 U.S.C. § 103:

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In meeting this burden we note that "the test for obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." In re Rosselet, 347 F.2d 847, 851, 146 USPQ 183, 186 (CCPA 1965).

According to the examiner (Answer, page 3) Chu and Prockop "teach the human proα1(I) procollagen and the N and C propeptides (see Fig. 3 in each)." The examiner relies on Olsen (Answer, page 3) to "teach the C-terminal propeptide of type I procollagen." The examiner relies on Carter (Answer, page 3) to teach "that a gene can be fused so as to produce fusion proteins and that

[2] Paper No. 29, mailed June 19, 1998. We note the Answer is incorrectly identified as Paper No. 27. Paper No. 27, mailed May 19, 1998 represents a Notification of non-compliance with the requirements of 37 CFR § 1.192(c). The Answer is Paper No. 29.
[3] Paper No. 28, received May 20, 1998.
[4] Paper No. 31, received August 24, 1998.
[5] Paper No. 32, mailed September 3, 1998.

these fusion proteins can be specifically cleaved using various chemical and enzymatic means (see Table I)."

According to the examiner (Answer, page 3):

> It would have been obvious to one of ordinary skill in the art to make a fusion protein that consisted of collagen and either the N or C-terminal propeptide, as taught in the primary references, using the methods taught in Carter, et. al. ... Whether or not a non-natural amino acid was used and which specific cleavage site and agent was used would have been obvious and well within the skill level of the ordinary artisan, absent unexpected results.

We note that appellants do not discuss Chu, Prockop or Olsen, beyond stating (Brief, page 4) that "[t]o the extent that these references are cited to show that procollagens, including their natural propeptide terminal portions are known in the art, Appellants concur." Instead, appellants focus their argument on the teachings of Carter.

Claims 1-3, 8-9, 14-16 and 18:

Appellants state (Brief, page 3) that "claims 1-3, 8-9, 14-16 and 18 shall stand as a group...." Accordingly, claims 1-3, 8, 9, 14-16 and 18 stand or fall together. Therefore, we limit our discussion to representative independent claim 1, claims 2-3, 8, 9, 14-16 and 18 will stand or fall together with claim 1. In re Young, 927 F.2d 588, 590, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

According to appellants (Brief, page 4) "procollagens already have fused propeptides and cleavage sites that enhance proper expression: nowhere does Carter suggest or motivate replacing a native propeptide with a different

DAVE TOMAN

propeptide or replacing the proteolytic cleavage site of an existing propeptide with a non-native site." In addition, appellants argue (Brief, page 5) that:

> [o]ne would have to turn Carter on its head to fuse a collagen propeptide to a collagen protein and then call it an "affinity handle". The whole point of Carter and affinity handles is to take a protein that doesn't provide a good binding target and stick a convenient tag on it. If collagen propeptides provided affinity tags, there would be no point in making a fusion protein – a suitable handle is already there.

In response, the examiner argues (Answer, page 4) that:

> [a]pplicants do not argue that putting two (or three) well known sequences together with a "non-natural site-specific proteolytic agent recognition site" between them would not have been obvious over the prior art but rather [they] argue that there would be no motivation to do so. As stated in the final rejection this construct could be made to purify the collagen with an affinity handle. This is taught in Carter, first paragraph. For instance, an antibody could be made to a particular procollagen, the construct of the instant claims could be put on an affinity column containing this antibody bound to a solid matrix, the contaminating proteins washed out and then the site-specific cleavage means could be employed to cleave the collagen molecule, thereby facilitating purification. This same procedure could also have been done batch-wise, not using a column.

The examiner further argues (Answer, bridging paragraph, pages 5-6) that:

> [o]ne could make a cleavage site that could be readily and easily cleaved using a site-specific cleavage means instead of using the cleavage means used in the processing of natural collagen, [sic]. This process[ing of natural collagen] uses enzymes thought to be expressed only in cells that naturally produce collagen. In addition, the use of the construct in a purification scheme involving solubility discussed supra has not been addressed by applicants.

As set forth in In re Soderquist, 326 F.2d 1016, 1018, 140 USPQ 387, 389 (CCPA 1964):

> It is not necessary in a combination rejection that the structure of one reference be substituted bodily in that of the reference with which it is combined. In re Billingsley, 47 CCPA 1108, 279 F.2d 689, 126 USPQ 370; In re Mason, 44 CCPA 727, 240 F.2d 362, 112 USPQ 328. Rather, the question is whether what applicant has done would be obvious from the references in combination.

In our opinion, on the record before us, the examiner has provided sufficient evidence to support a conclusion that the claimed subject matter would have been prima facie obvious within the meaning of 35 U.S.C. § 103.

We do not agree with appellants' argument (Brief, page 5) that "[i]f collagen propeptides provided affinity tags, there would be no point in making a fusion protein – a suitable handle is already there." As explained by the examiner (Answer, pages 4-6) using a site-specific cleavage means as taught by Carter would facilitate purification and would not require the natural collagen processing enzymes that are thought to be expressed only in cells that naturally produce collagen.

We note appellants' emphasis (Brief, page 5) that "[a]ll the pending claims require (1) a C-terminal propeptide, whereas the affinity handles of Carter are all N-terminal fusions...." In response to this position, the examiner explains (Answer, page 5) that the claims "only require that the 'first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide', not that the affinity handle be a C-fusion." We note that appellants withdrew their remarks regarding this issue in the Reply Brief.

Accordingly, we affirm the rejection of claim 1 under 35 U.S.C. § 103 as being unpatentable over Chu, Prockop and Olsen in view of Carter. As discussed supra claims 2, 3, 8, 9, 14-16 and 18 fall together with claim 1.

Claims 6 and 7:

According to appellants (Brief, page 5):

> [c]laims 6 and 7 further limit claim 1 to require a second propeptide and a second non-natural site-specific proteolytic agent recognition site located between the collagen chain and the second propeptide. As there is no suggestion whatsoever in the cited art of using a second recognition site and a second propeptide, the rejection of claims 6 and 7 under 35 U.S.C. [sic] [§] 103 is improper.

Initially, we note that the examiner failed to address these limitations in his statement of the rejection (Answer, page 3). Further, while explaining how the combination of Chu, Prockop and Olsen in view of Carter meet the limitations of claims 1, 2, 3, 8, 9, 14-16 and 18, the examiner states (Answer, page 5) that "[t]he same is true of claims 6 and 7 where the C-terminal propeptide and the second propeptide could be located at either end of the collagen, or the two propeptides could both [be] located at one end of the collagen [chain]." The examiner, however, fails to identify a suggestion in the art to prepare such a construct.

As discussed above, we agree with the examiner that, in view of the combination of prior art relied upon it would have been prima facie obvious at the time the invention was made to prepare a collagen chain fusion that is substantially the same as the native procollagen molecule but for the presence

of a "non-native" site-specific proteolytic agent recognition site located between the collagen chain and the propeptide, as set forth in claims 1, 2, 3, 8, 9, 14-16 and 18. We agree with the examiner that, in view of the combination of prior art relied upon a person of ordinary skill in the art would recognize that such a construction would facilitate purification (Answer, page 4), and allow the use of alternative means, as taught by Carter, for cleaving the propeptide from the collagen chain, than those "enzymes though to be expressed only in cells that naturally produce collagen" (Answer, page 5).

In contrast, we can not agree with the examiner's position that, in view of the combination of prior art relied upon a person of ordinary skill in the art would recognize that a "second propeptide could be located at either end of the collagen, or the two propeptides could be located at one end of the collagen" (Answer, page 5). While a person of ordinary skill in the art may possess the requisite knowledge and ability to make the modifications suggested by the examiner, the modifications are not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). Here we see no reason, and the examiner failed to identify a reason in the art, to suggest that a person of ordinary skill in the art would modify the references to include a second propeptide and a second non-natural site-specific proteolytic agent recognition site.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444

(Fed. Cir. 1992). On these circumstances, we are constrained to reach the conclusion that the examiner has failed to provide the evidence necessary to support a prima facie case of obviousness. Accordingly, we reverse the rejection of claim 6 under 35 U.S.C. § 103 as being unpatentable over Chu, Prockop and Olsen in view of Carter. As discussed supra claim 7 stands together with claim 6.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

DONALD E. ADAMS)
Administrative Patent Judge)
)
)
DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
) INTERFERENCES
ERIC GRIMES)
Administrative Patent Judge)

C4H-018-D1

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 18

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RICHARD A. BERG, PAUL D. TOMAN and DONALD G. WALLACE

MAILED

APR 30 2001

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 1999-1706
Application No. 08/630,654

ON BRIEF

Before ADAMS, MILLS and GRIMES, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 21-30, which are all the claims pending in the application.

Claim 21 is illustrative of the subject matter on appeal and is reproduced below:

21. A nucleic acid encoding a recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen polypeptide chain and said first propeptide, and said propeptide is located at the C-terminus of said procollagen polypeptide chain.

The references relied upon by the examiner are:

Prockop et al. (Prockop) WO 93/07889 Apr. 29 1993

Carter, "Site-Specific Proteolysis of Fusion Proteins," Protein Purification: From Molecular Mechanisms to Large-Scale Processes, Vol. 47, Chp. 13, pp. 181-193 (American Chemical Society 1990)

Ryan et al. (Ryan), "The Human Type II Procollagen Gene: Identification of an Additional Protein-Coding Domain and Location of Potential Regulatory Sequences in the Promoter and First Intron," Genomics, Vol. 8, pp. 41-48 (1990)

GROUND OF REJECTION

Claims 21-30 stand rejected under 35 U.S.C. § 103 as being unpatentable over Ryan in view of Prockop and Carter.

We affirm.

DISCUSSION

In reaching our decision in this appeal, we considered appellants' specification and claims, in addition to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer[1], for the examiner's reasoning in support of the rejections. We further reference appellants' Brief[2], and appellants' Reply Brief[3] for the appellants' arguments in favor of patentability. We note the examiner considered the Reply Brief, and entered it into the record.[4]

[1] Paper No. 14, mailed June 19, 1998.
[2] Paper No. 12, received May 11, 1998.
[3] Paper No. 16, received August 24, 1998.
[4] Paper No. 17, mailed September 1, 1998.

CLAIM GROUPING:

Appellants state (Brief, page 3) that "claims 21-30 shall stand as a group." Accordingly, claims 21-30 stand or fall together. Therefore, we limit our discussion to representative independent claim 21. Claims 22-30 will stand or fall together with claim 21. In re Young, 927 F.2d 588, 590, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991).

THE REJECTION UNDER 35 U.S.C. § 103:

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In meeting this burden we note that "the test for obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." In re Rosselet, 347 F.2d 847, 851, 146 USPQ 183, 186 (CCPA 1965).

According to the examiner (Answer, page 3) Ryan "teach a nucleic acid encoding a recombinant procollagen chain comprising a natural collagen polypeptide chain (figure 2, pages 44-45)." The examiner relies on Prockop (Answer, page 4) to "teach a vector comprising a recombinant human procollagen gene, a transcription regulatory element ... (figure 4 and table 1), and a C-propeptide and an N-propeptide (figure 4)." The examiner relies on Carter (Answer, page 4) to teach "the use of non-natural site-specific proteolytic agent recognition sites in fusion proteins to generate site-specifically cleaved

proteins by recombinant DNA techniques (abstract, table 1, table 2, table 3, table 4, table 5, table 6, [and] table 7)."

According to the examiner (Answer, bridging paragraph, pages 4-5):

> Recombinant gene expression can become difficult to obtain if the protein normally requires extensive post-translational processing, as is the case with collagen (Prockop et al. page 1). The propeptides of procollagen are normally cleaved during processing of the gene product to mature collagen. The C-terminal propeptide of procollagen is required for proper chain assembly of collagen molecules. Since collagen is a triple helical molecule, proper chain assembly is critical for the production of biologically active collagen. A person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as it is found in nature, a properly folded recombinantly produced procollagen molecule could be produced. However, the ordinary artisan would be aware of the fact that production of mature collagen would require removal of this C-terminal propeptide. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen between the regions encoding collagen and the C-terminal propeptide, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan and which would be prechosen by designing the appropriate sequences into the hybrid protein.

The examiner reasons (Answer, page 5) that:

> [b]y designing an artificial protease site into the procollagen chain between the C-terminal propeptide and the collagen chain, the skilled artisan would not have to rely on using the naturally-occurring protease which cleaves the C-terminal propeptide from the collagen chain. Host cells such as bacteria, yeast or insect cells which do not naturally produce this mammalian protease could then be used to produce mature collagen because they could be engineered to produce the protease specific for the site designed into the procollagen chain of the instant invention."

We note, as does the examiner (Answer, page 6), that appellants do not discuss Ryan or Prockop, beyond stating (Brief, page 3) that "Ryan and Prockop describe a procollagen gene and a procollagen vector." Instead, appellants focus their argument on the teachings of Carter. According to appellants (Brief, page 4) "procollagens already have fused propeptides and cleavage sites that enhance proper expression: nowhere does Carter suggest or motivate replacing a native propeptide with a different propeptide or replacing the proteolytic cleavage site of an existing propeptide with a non-native site." In addition, appellants argue (Brief, page 4) that:

> [o]ne would have to turn Carter on its head to fuse a collagen propeptide to a collagen protein and then call it an "affinity handle". The whole point of Carter and affinity handles is to take a protein that doesn't provide a good binding target and stick a convenient tag on it. If collagen propeptides provided affinity tags, there would be no point in making a fusion protein – a suitable handle is already there.

In response, the examiner argues (Answer, page 6) that:

> [m]otivation for combining the work of Ryan et al., Prockop et al. and Carter can be found in the work of Prockop et al. and Carter. Recombinant gene expression can become difficult to obtain if the protein normally requires extensive post-translational processing, as is the case with collagen (Prockop et al. page 1).

The examiner further argues (Answer, page 7) that appellants "have not addressed the motivation cited above pertaining to post-translational processing

of the procollagen peptide (set forth in the first office action)." In addition, the examiner argues (Answer, bridging paragraph, pages 7-8) that:

> [A] person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as it is found in nature, a properly folded recombinantly produced procollagen molecule could be produced. This is because the C-terminal propeptide is necessary for proper chain assembly of collagen molecules. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan [as taught by Carter].... [T]he key to affinity purification is the ability to easily and efficiently remove bound target protein from an affinity column. Including a non-natural cleavage site in the procollagen construct would give the skilled artisan the ability to choose by what means cleavage of the collagen chain from the C-terminal propeptide was to be achieved and would give such an artisan the flexibility to weigh parameters such as the expense of the chemical or enzymatic agent to be used, the harshness of the conditions, the specificity of the cleavage agent and the efficiency of the agent.

As set forth in In re Soderquist, 326 F.2d 1016, 1018, 140 USPQ 387, 389 (CCPA 1964)

> It is not necessary in a combination rejection that the structure of one reference be substituted bodily in that of the reference with which it is combined. In re Billingsley, 47 CCPA 1108, 279 F.2d 689, 126 USPQ 370; In re Mason, 44 CCPA 727, 240 F.2d 362, 112 USPQ 328. Rather, the question is whether what applicant has done would be obvious from the references in combination.

In our opinion, on the record before us, the examiner has provided sufficient evidence to support a conclusion that the claimed subject matter would have been prima facie obvious within the meaning of 35 U.S.C. § 103. We agree with the examiner, as discussed supra, that by designing a non-natural site-specific proteolytic agent recognition site into the procollagen chain the

skilled artisan would not have to rely on using the naturally occurring protease which cleaves the C-terminal propeptide from the collagen chain. Instead, the skilled artisan would have the ability to choose by what means cleavage of the collagen chain from the C-terminal propeptide was to be achieved and would have the flexibility to weigh parameters such as expense, conditions, specificity and efficiency.

We are not persuaded by appellants' argument (Reply Brief, page 1) that the "Answer's suggestion (p. 8, line 17- p.9, line 5) for replacing Carter's N-terminal affinity handles with C-terminus fusions derives from [a]pplicants' [sic] disclosure and is contrary to the repeated and exclusive teachings of Carter (e.g.[,] Carter, p.1, first paragraph and p.2, first paragraph)." As the examiner explains (Answer, page 9) "[t]he C-terminal propeptide is required for proper chain assembly of collagen and the skilled artisan would have no reason to move the C-terminal propeptide [to] the N-terminus."

Accordingly, we affirm the rejection of claim 21 under 35 U.S.C. § 103 as being unpatentable over Ryan in view of Prockop and Carter. As discussed supra claims 22-30 fall together with claim 21.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

DONALD E. ADAMS)
Administrative Patent Judge)
)
)
DEMETRA J. MILLS) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
ERIC GRIMES) INTERFERENCES
Administrative Patent Judge)

United States Court of Appeals for the Federal Circuit

02-1120, -1160
(Serial nos. 08/630,654, 08/278,774)

IN RE RICHARD A. BERG,
PAUL D. TOMAN, and DONALD G. WALLACE

DECIDED: February 20, 2003

Before BRYSON, Circuit Judge, PLAGER, Senior Circuit Judge, and PROST, Circuit Judge.

BRYSON, Circuit Judge.

Appellants Richard A. Berg, Paul D. Toman, and Donald G. Wallace seek review of two decisions of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, one sustaining a rejection of the appellants' application as obvious under 35 U.S.C. § 103(a) and the other upholding the rejection of a related divisional application for the same reason. We affirm.

I

In 1994, the appellants filed a patent application, Serial No. 08/278,774 ("the '774 application"), claiming "Mutated Recombinant Collagens." Independent claim 1 is representative of the claimed subject matter:

> 1. A recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen chain and said first propeptide.

The appellants subsequently filed a divisional application, Serial No. 08/630,654 ("the '654 application"), claiming nucleic acids that encode the proteins claimed in the '774 application. Independent claim 21 is illustrative of the subject matter of the divisional application:

> 21. A nucleic acid encoding a recombinant procollagen polypeptide chain comprising a natural collagen polypeptide chain, a first natural procollagen C-terminal propeptide and a first non-natural site-specific proteolytic agent recognition site, wherein said first non-natural site-specific proteolytic agent recognition site is located between said collagen polypeptide chain and said first propeptide, and said propeptide is located at the C-terminus of said procollagen polypeptide chain.

The patent examiner who reviewed the two applications rejected certain claims in each application for obviousness. For the '774 application, the examiner concluded that independent claim 1 and dependent claims 2-3, 6-9, 14-16, and 18 were unpatentable over four prior art references—Chu, Prockop, and Olsen in view of Carter. For the '654 application, the examiner rejected independent claim 21 and dependent claims 22-30 as unpatentable over three prior art references—Ryan in view of Carter and Prockop II, a different reference by Prockop. The appellants appealed the rejections to the Board.

The Board agreed with the examiner that Chu, Prockop, and Olsen in view of Carter established an unrebutted prima facie case of obviousness for all but two of the appealed claims of the '774 application, and that Ryan in view of Carter and Prockop II established an unrebutted prima facie case of obviousness for all of the appealed claims of the '654 application. Accordingly, the Board affirmed the examiner's rejection of the claims that are at issue in this appeal. The Board subsequently denied the appellants' requests for reconsideration, and this appeal followed.

II

Collagen is a natural protein found in humans and, in somewhat different form, in other animals. It has been used in a wide range of applications, including as a substrate for cell cultureware and in human reconstructive therapy. As the major macromolecule in most human connective tissue, collagen has many potential therapeutic applications. Because of difficulties encountered in obtaining and using non-human collagen or human collagen from cadavers and placentas, it has been considered desirable to produce human collagen as a recombinant protein expressed in E. coli bacteria.

When collagen is synthesized, it is typically expressed as a precursor, procollagen, which consists of collagen with additional peptide extensions at either end of the molecular chain, i.e., at the amino and carboxyl ends (also known as the N-terminus and the C-terminus). The peptide extensions are then removed by specific proteolytic enzymes, known as proteases, to produce collagen.

The claimed invention is a polypeptide chain in which a natural procollagen C-terminal propeptide is fused to a collagen peptide via a non-natural site-specific proteolytic agent recognition site, i.e., a site at which a particular protease can cleave the peptide chain into two pieces. The natural procollagen C-terminal propeptide is useful in folding the peptide into its proper shape, but after the folding process is complete, the C-terminal propeptide can be cleaved off by an appropriate enzyme and purified out of the composition, leaving only the mature collagen.

III

Obviousness is a question of law supported by underlying facts. In re Gartside, 203 F.3d 1305, 1316, 53 USPQ2d 1769, 1776 (Fed. Cir. 2000). What the prior art teaches and whether it teaches away from the claimed invention are questions of fact. In re Bell, 991 F.2d 781, 784, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). On appeal, the Board's factual findings are reviewed for substantial evidence. Gartside, 203 F.3d at 1316, 53 USPQ2d at 1776. Because the appellants' arguments focus on the teachings of the prior art, our obviousness inquiry focuses on whether the Board's factual conclusions as to those teachings are supported by substantial evidence.

Because the appellants treat the two related applications together, we do the same. With respect to the '774 application, the appellants did not argue dependent claims 2-3, 8-9, 14-16, or 18 separately to the Board, nor do they in this appeal. The rejected claims therefore stand or fall with representative independent claim 1. With respect to the '654 application, the appellants did not argue dependent claims 22-30 of that application separately to the Board or to us, so the rejected claims stand or fall with representative independent claim 21. See In re Dance, 160 F.3d 1339, 1340 n.2, 48 USPQ2d 1635, 1636 n.2 (Fed. Cir. 1998).

In the prosecution of the '774 application, the examiner found that Chu and Prockop teach human procollagen and its N- and C-terminal propeptides, and that Olsen teaches the C-terminal propeptide of type 1 procollagen. In addition, the examiner relied on Carter as teaching that genes can be engineered so as to produce fusion proteins, and that those fusion proteins can be specifically cleaved using various chemical and enzymatic means. In the prosecution of the '654 application, the

examiner found that Ryan teaches a nucleic acid sequence encoding a recombinant procollagen chain comprising a natural collagen polypeptide chain. In addition, the examiner concluded that Prockop II contains the following disclosures: (1) a vector comprising a recombinant human procollagen gene; (2) a promoter not naturally linked to the recombinant gene, and (3) the C-propeptide and N-propeptide of procollagen. The examiner further explained that the C-terminal propeptide is necessary for proper chain assembly of collagen molecules, a teaching found in the Prockop reference. The Board affirmed the examiner's interpretation of each of the prior art references, and the appellants do not challenge those interpretations.

Based on the prior art references of record, the examiner concluded that it would have been obvious to a person of ordinary skill in the art to create a recombinant DNA system for the production of procollagen in which the recombinant procollagen chain consisted of a natural collagen polypeptide and a first natural propeptide, with a first non-natural site-specific proteolytic agent recognition site located between them. It is that conclusion to which the appellants object.

The appellants do not dispute that procollagens (including their natural N- and C-terminal propeptides) and the genes that encode them are well known in the art. Instead, they challenge the conclusion of the examiner and the Board that Carter provided the motivation for the inventions claimed in the two applications. The examiner and the Board viewed Carter broadly, as disclosing that two proteins can be fused together for a variety for reasons, and that once those proteins are expressed they can be chemically or enzymatically separated at specific sites on the protein chain. Based on that teaching, the examiner and the Board concluded that the prior art made

it obvious that one could engineer a gene to code for a natural collagen polypeptide chain fused with a natural procollagen C-terminal propeptide via a non-natural site-specific proteolytic agent recognition site, and that, once expressed, the two proteins could be separated enzymatically or chemically by particular known agents at that site. As the examiner explained: "One could make a cleavage site that could be readily and easily cleaved using a site-specific cleavage means instead of using the cleavage means used in the processing of natural collagen." Thus, both the examiner and the Board concluded that because it was well known from the prior art that two proteins could be fused at a particular cleavage site, and because the sequences and properties of procollagen and collagen were well known, it would have been obvious to fuse the natural collagen peptide with the natural procollagen C-terminal propeptide at a cleavage site that would respond to an enzyme other than one found naturally within the human body. The examiner explained this point in some detail:

> The propeptides of procollagen are normally cleaved during processing of the gene product to mature collagen. The C-terminal propeptide of procollagen is required for proper chain assembly of collagen molecules. Since collagen is a triple helical molecule, proper chain assembly is critical for the production of biologically active collagen. A person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as it is found in nature, a properly folded recombinantly produced procollagen molecule could be produced. However, the ordinary artisan would be aware of the fact that production of mature collagen would require removal of this C-terminal propeptide. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen between the regions encoding collagen and the C-terminal propeptide, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan and which would be prechosen by designing the appropriate sequence into the hybrid protein.

The examiner further stated that by designing an artificial proteolytic agent recognition site into the procollagen chain between the C-terminal propeptide and the collagen

chain, the skilled artisan would not have to rely on using the naturally occurring protease that cleaves the C-terminal propeptide from the collagen chain. Thus, the examiner explained, the host cells that would be relied on to manufacture the hybrid protein, which do not naturally produce the requisite mammalian protease, could be used to produce mature collagen by being engineered to produce the protease specific for the site designed into the procollagen chain.

The appellants argue that Carter does not provide the necessary motivation to create a protein consisting of a natural collagen chain separated from a natural procollagen C-terminal propeptide by a non-native cleavage site. They read Carter narrowly, treating it primarily as a discussion of the use of "affinity handles," which Carter teaches are polypeptides with a high affinity for a particular ligand that can be used for purification of fusion proteins. They further argue that to the extent the examiner reasoned that Carter suggests the use of the procollagen C-terminal propeptide as an affinity handle to purify the collagen, no person of ordinary skill in the art would read Carter in that manner. That is because, the appellants explain, collagen-specific antibodies are widely known and commercially available, and a skilled artisan would therefore not use an affinity handle to purify collagen.

The appellants further argue that even if there were no available collagen-specific antibodies, Carter would, at most, suggest genetically engineering an affinity handle onto the collagen. The appellants explain that because there are many well-known affinity handles with high affinity ligands that can be used for purification, Carter would not suggest using a natural procollagen C-terminal propeptide in the place of one of those known affinity handles.

Although the appellants' criticism of the Board's discussion of Carter focuses on Carter's specific teachings with respect to affinity handles, that was not the exclusive basis on which the Board found Carter to be relevant to the obviousness inquiry. Thus, while the appellants argue that procollagens are not affinity handles as Carter describes them, that contention does not undermine the Board's conclusion that the more general teachings of Carter as to fusion proteins, combined with the prior art teachings as to the structure, function, and synthesis of procollagen and collagen, render the appellants' claimed inventions obvious. The examiner and the Board found that the prior art references, including Carter, provided the motivation to fuse the natural collagen chain and the C-terminal propeptide at a non-native cleavage site. As noted above, the examiner and the Board found that the C-terminal propeptide provides benefits in post-translational processing of the procollagen peptide, which a person of ordinary skill in the art would have been motivated to preserve. The examiner summarized that motivation as follows:

> A person having ordinary skill in the art would recognize that by keeping the C-terminal propeptide at the C-terminus of the procollagen chain, as found in nature, a properly folded recombinantly produced procollagen molecule could be produced. This is because the C-terminal propeptide is necessary for proper chain assembly of collagen molecules. By including a non-natural site-specific proteolytic agent recognition site in the genetic construct for expressing procollagen, the resultant hybrid protein could be cleaved using a number of enzymatic or chemical means at the disposal of the skilled artisan and which would be prechosen by designing the appropriate sequence into the hybrid protein.

The examiner found that the prior art gave rise to a second motivation for making the claimed fusion protein with a non-natural site-specific cleavage site located between the C-terminal propeptide and the collagen chain—to simplify purification of the synthesized product. The examiner explained:

> Including a non-natural cleavage site in a procollagen construct would give the skilled artisan the ability to choose by what means cleavage of the collagen chain from the C-terminal propeptide was to be achieved and would give such an artisan the flexibility to weigh parameters such as the expense of the chemical or enzymatic agent to be used, the harshness of the conditions, the specificity of the cleavage agent and the efficiency of the agent.

The Board upheld these findings as to the motivation to make the fused protein of the asserted claims. The appellants insist that the examiner and the Board erred in finding a prima facie case of obviousness because, the appellants contend, the prior art references would not provide a person of ordinary skill in the art with the motivation to make the claimed inventions. The appellants, however, have not pointed to any clear flaw in the reasoning of the examiner and the Board on this issue, nor have they pointed to any evidence of record indicating that the findings of the examiner and the Board on this issue are unsupportable.

As persons of scientific competence in the fields in which they work, examiners and administrative patent judges on the Board are responsible for making findings, informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art and the motivation those references would provide to such persons. Absent legal error or contrary factual evidence, those findings can establish a prima facie case of obviousness. In this case, the appellants have not pointed to any legal error affecting the Board's obviousness analysis. Nor have they pointed to sufficient factual grounds, either in the record or in any judicially noticeable sources, to question the findings made by the examiner and the Board as to the teachings of the prior art and the motivation that the prior art references would give to a skilled artisan to make the claimed invention. We therefore sustain the Board's

conclusion that the recited prior art references established a prima facie case of obviousness with respect to the appealed claims of the '774 and '654 applications.

IV

The appellants attempt to rebut the prima facie case of obviousness by arguing that the prior art teaches away from their claimed inventions. See In re Haruna, 249 F.3d 1327, 1335, 58 USPQ2d 1517, 1522 (Fed. Cir. 2001). They contend that prior art references such as Prockop II disclose that expression of recombinant collagen in systems that do not naturally express the requisite procollagen-modifying enzymes requires the artisan to engineer the cells to express the necessary processing enzymes rather than engineering the collagen genes themselves to facilitate processing. The appellants fail to demonstrate, however, how re-engineering the cells to facilitate processing instead of engineering the collagen genes teaches away from their approach. Specifically, they do not explain how the disclosures of the prior art show that their claimed invention is unlikely to be productive of the desired result. See In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). The mere fact that there is an alternative means of expressing recombinant collagen in the prior art does not preclude the development of a new model that is obvious over the prior art. See In re Beattie, 974 F.2d 1309, 1312-13, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (holding that an alternative to a well-entrenched theory does not preclude a finding of obviousness because the recommendation of a new system "does not require obliteration of another"). The appellants' arguments that the prior art teaches away from their claimed invention are thus without merit.

V

Because the appellants have not shown why the Board's conclusions regarding the disclosures in the prior art are not supported by substantial evidence, we agree that Chu, Prockop, and Olsen in view of Carter create a prima facie case of obviousness of claims 1-3, 8-9, 14-16, and 18 of the '774 application and that Ryan in view of Carter and Prockop II constitutes a prima facie case of obviousness for claims 21-30 of the '654 application. Because the appellants did not present persuasive evidence or argument in rebuttal, see In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984), we affirm the decisions of the Board rejecting these claims.

AFFIRMED.

EVIDENCE APPENDIX

None.